Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-29 and 44-50 are pending in the application, with claims 1 and 49 being the independent claims. Claims 30-43 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Support for the amendment to claim 1 can be found, *inter alia*, in the specification at pages 6, 10, 36, 66, and 71-74. Support for new claims 49 and 50 can be found in the original claims 2, 19, 25, and 48. These changes are believed to introduce no new matter. Their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112

In the Office Action at page 2, the Examiner has rejected claims 1-3, 7, 10-18, 24, 26-28, and 44-48 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner has taken the position that:

> [i]n the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise the wild type MMLV reverse transcriptase as

> shown by the prior art sequence modified at the selected positions as having enhanced thermostability.

Office Action, page 5, lines 20-25. Applicants respectfully disagree.

Claims 1-29 are drawn to a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223. Claims 44-48 further specify kits comprising said reverse transcriptases.

The present specification provides a number of examples of reverse transcriptases that can be used in the practice of the invention. *See, e.g.,* specification at pages 6, 8-9, and 30. The sequences of these exemplary reverse transcriptases including M-MLV are known in the art. Numerous patents and other publications describing such reverse transcriptases have been incorporated into the specification by reference. *See*, *e.g.*, specification at pages 3-4, 34 and 76. In addition, the specification identifies the claimed functional characteristics, *i.e.*, increased or enhanced thermostability or fidelity, reduced or eliminated misincorporation, and reduced or substantially reduced terminal deoxynucleotidyl transferase activity (*see, e.g.,* specification at pages 5-10 and 23-29). Moreover, the specification identifies the relevant structural features that correlate to these functions. For example, the regions corresponding to areas of fidelity which may interact with template-primer during nucleic acid extension are provided for a number of reverse transcriptases, including M-MLV (*see, e.g.,* specification at pages 8-9, Table 1). The specification also provides guidance as to the types of mutations that can be

introduced in the thumb, fingers and palm regions of at least two exemplified reverse transcriptases (HIV and M-MLV) in order to impart particular physical and functional characteristics to the claimed reverse transcriptases (*see, e.g.,* specification at page 29). Finally, the present specification provides examples of one or more functional embodiments of the presently claimed invention, thereby providing a reduction to practice consistent with the Federal Circuit's holding in *Fiers v. Sugano* (*see* Office Action at page 5, lines 3-8). *See, e.g.,* Examples at pages 60-76.

Applicants respectfully submit that based on the disclosures contained in the present specification, one of ordinary skill in the art would readily recognize that Applicants, at the time the present application was filed, had possession of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. § 102

In the Office Action at page 6, the Examiner has rejected claims 1, 16, 17, 18, 24, and 26-28 under 35 U.S.C. § 102(b) as allegedly anticipated by Blain *et al.* (*J. Biol. Chem. 268*:23585-2392 (1993), PTO-892 document U). Applicants respectfully traverse this rejection.

The Examiner has taken the position that "relative to completely inactive fragments, the mutant MMLV reverse transcriptases shown by Blain have increased fidelity and thermostability while they have reduced RNAseH [sic] activity relative to wild type MMLV reverse transcriptase." *See* Office Action at page 7, lines 2-5. Applicants respectfully disagree.

Claims 1-29 are drawn to a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). This burden is not met by the disclosure of Blain *et al.* who do not teach or suggest a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223. Therefore, the claimed invention is not anticipated by Blain *et al.* Withdrawal of this rejection is respectfully requested.

In the Office Action at page 7, the Examiner has rejected claims 1, 12-18, 24, and 26-28 under 35 U.S.C. § 102(a) as allegedly anticipated by Arakawa *et al.* (Japanese patent application 2000-139457, PTO-892 document N). Applicants respectfully traverse

this rejection.

Specifically, the Examiner contends that Arakawa *et al.* disclose "altered MMLV reverse transcriptases which have expressly shown reduced RNAse H activity . . . which retains enhanced DNA polymerase activity . . . and expressly teaches thermostability at 60 C [sic] of the modified enzyme which retains significant activity at 60 C [sic]." Office Action at page 7, lines 8-12. Applicants respectfully disagree.

Applicants first note that Arakawa's modified M-MLV RT amino acid coding sequence appears to begin at the first translated methionine. However, one skilled in the art recognizes that the first translated coding sequence for M-MLV protein is not methionine, but threonine. *See, e.g.*, specification at page 60, paragraph 0161.

It appears that Arakawa's mutant M-MLV RT is mis-aligned by one amino acid. For example, Arakawa specifically discloses a M-MLV reverse transcriptase having a point mutation at amino acid valine 224. However, one skilled in the art recognizes that the amino acid position valine occupies amino acid position 223 between the tyrosine and aspartic acids of the YXDD motif discussed by Arakawa. Arakawa's mutation of valine to methionine at this position was shown to "improve the elongation during cDNA synthesis at 60°C." (See the unverified English translation of JP P2000-139457, page 5, paragraph 0008, cited herewith as IDS document AR16). Arakawa also discloses a mutation at amino acid aspartic acid 584 (or aspartic acid 583). This mutation reduced RNase H activity. See, *e.g.*, JP P2000-139457, page 5, paragraph 0008.

Arakawa does not teach or suggest a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance

thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223. Therefore, the claimed invention is not anticipated by Arakawa. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

In the Office Action at page 8, the Examiner has rejected claims 44-47 under 35 U.S.C. § 103(a) as allegedly unpatentable over Blain *et al.*, *cited supra*, or Arakawa *et al.*, *cited supra*, in view of Stratagene Catalog, page 39 (1988) . Applicants respectfully traverse this rejection.

The Examiner contends that:

> [i]t would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method and products of either Blain or Arakawa into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit.

Office Action, page 9, lines 1-4. Applicants respectfully disagree.

Claims 1-29 are drawn to a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223. Claims 44-48 further specify kits comprising said reverse transcriptases.

Blain *et al.* disclose wild-type MMLV with increased activity over inactive fragments. Arakawa *et al.* specifically disclose a methionine mutation at amino acid valine 224 (which is actually valine 223) of M-MLV reverse transcriptase. Neither of these references teach or suggest kits comprising a reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223. This deficit is not cured by page 39 of the Stratagene catalog which mentions different types of kits but does not teach or suggest the invention as claimed. Therefore, a *prima facie* case of obviousness has not been established based on the cited references, either alone or in combination. Withdrawal of this rejection is respectfully requested.

Other Matters

Applicants note that they have not received the Examiner-initialed copy of the form PTO-1449 (15 sheets) submitted with Applicants' IDS filed on November 2, 2001, and form PTO-1449 (15 sheets) submitted with Applicants First Supplemental IDS filed on June 25, 2002. Enclosed herewith is a courtesy copy of the post card receipts, IDSs and forms 1449 filed on November 2, 2001 and June 25, 2002. It is respectfully requested that the Examiner initial and return a copy of the forms PTO-1449 which were filed on November 2, 2001 and June 25, 2002, and indicate in the official file wrapper of this patent application that these cited documents have been considered.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 30-43 have been cancelled.

New claims 49-50 are sought to be added.

Claim 1 has been amended as follows:

1. (Once amended) A reverse transcriptase having reverse transcriptase activity which has been modified or mutated to increase or enhance thermostability wherein said mutation or modification that increase or enhance thermostability is not in the RNase H domain with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223.